experimental data for MMTV and hTR. The equilibrium free energy profiles, which predict the structural transitions that occur at each melting temperature, are used to propose that the relative stabilities of the isolated helices control their folding mechanisms. Kinetic simulations, which corroborate the inferences drawn from the free energy profiles, show that MMTV folds by a hierarchical mechanism with parallel paths i.e., formation of one of the helices nucleates the assembly of the rest of the structure. The SRV-1 pseudoknot folds in a highly cooperative manner and assembles in a single step in which the preformed helices coalesce nearly simultaneously to form the tertiary structure. Folding occurs by multiple pathways in the hTR pseudoknot, whose isolated structural elements have similar stabilities. In one of the paths, tertiary interactions are established prior to the formation of the secondary structures. Our work shows that there are significant sequence-dependent variations in the folding landscapes of RNA molecules with similar fold. We also establish that assembly mechanisms can be predicted using the stabilities of the isolated secondary structures.

2450-Pos
Mechanical Folding Kinetics of RNA Hairpins: a New Computational Approach
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From the distribution of the low-lying states on the energy landscape, we recently developed a new computational method for the prediction of RNA folding kinetics [1]. The method can treat long sequences because it is based on a small ensemble of seed states. Additionally, the method is based on an analytic formalism and thus enables predictions for long-time folding kinetics. Applications of the new kinetic model to mechanical folding of RNA hairpins reveal distinct kinetic behaviors for a wide range of different force regimes, from zero force to forces much stronger than the critical force for the folding-unfolding transition. In the low force limit, folding can be initiated (nucleated) at any position by the formation of the first base stack and folding can proceed through many parallel pathways. In contrast, for a higher force, the folding/unfolding would predominantly proceed along a single zipping/unzipping pathway. Studies for different hairpin-forming sequences indicate that depending on the nucleotide sequence, a kinetic intermediate can emerge in the low force regime but disappear in high force regime, and a new kinetic intermediate, which is absent in the low and high force regimes, can emerge in the medium force range. Variations of the force lead to changes in folding cooperativity and rate-limiting steps. For TAR RNA sequence, we predicted two parallel dominant pathways. The rate-limiting folding steps (at $f = 8$ pN) are the formation of specific base pairs that are 2-4 base pairs away from the loop. At a higher force ($f = 11$ pN), the folding rate is controlled by the formation of the bulge loop. The predicted rates and transition states are in good agreement with the experimental data for a broad force regime.
[1] Cao and Chen, 2009, *Biophys. J.*, **96**, 4024-4034.

2451-Pos
First-Principles Prediction of the Sequence-Dependent Stability of RNA Hairpin Loop
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We develop a statistical mechanical model to predict the sequence-dependent folding stability from the sequence for simple RNA hairpin loops. We use a recently developed 3-vector virtual bond-based RNA folding model which enables rigorous computation of RNA chain entropy. Enumeration of all the possible arrangements of base pairs and the corresponding conformational entropies, through exhaustive self-avoiding random walks of the virtual bonds in a diamond lattice, gives the partition function and free energy for a given RNA sequence. The new model developed here has two unique advantages. First, the model is based on the complete conformational ensemble, including loop conformations that contain all the possible intra-loop base pairs and/or terminal mismatches. Therefore, intra-loop base pairs and mismatches are the results predicted from the model instead of known input information for the model. Second, the model gives accurate estimation for the dramatic entropic changes caused by the formation of the intra-loop base pairs and mismatches. Our first principles calculations for the chain entropy for each given set of base pairs, in combination with the empirical energy function provided from Turner rules, provide ab initio predictions for the sequence-dependent loop stability from RNA sequence. Tests against experimental data indicate that the theory can give improved predictions for the sequence-dependent RNA hairpin loop stability than the nearest-neighbor model.

2452-Pos
Salt Dependent Folding Energy Landscape of RNA Three-Way Junction
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RNAs are highly negatively charged molecules. Salt ions are crucial for RNA folding stability and conformational changes. In the present work, we employ the recently developed tightly bound ion (TBI) model, which accounts for the inter-ion correlations and the fluctuation of ion distributions, to investigate the ion-dependent free energy landscape for the three-way RNA junction in a 16S rRNA domain. The predicted electrostatic free energy landscape suggests that (a) ion-mediated electrostatic interactions cause an ensemble of unfolded conformations narrowly populated around the maximally extended structure and (b) Mg2+ ion-induced correlation effect may help bring the helices to the folded state. Non-electrostatic interactions, such as non-canonical interactions within the junctions and between junctions and helix stems, might further limit the conformational diversity of the unfolded state, resulting in a more ordered unfolded state than the one predicted from the electrostatic effect. Moreover, the folded state is predominantly stabilized by the coaxial stacking force. The TBI-predicted folding stability agrees well with the experimental measurements for the different Na+ and Mg2+ ion concentrations. For Mg2+ solutions, the TBI model, which accounts for the ion correlation effect, gives more accurate predictions than the Poisson-Boltzmann theory, which tends to underestimate the role of Mg2+ in stabilizing the folded structure. Detailed control tests in-dicate that the dominant ion correlation effect comes from the charge-charge Coulombic correlation rather than the excluded volume (size) correlation between the ions. Furthermore, the model gives quantitative predictions for the ion size effect in the folding stability.

Chromatin

2453-Pos
Diffusion Based Looping of Chromatin
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Chromatin folding inside the interphase nucleus of eukaryotic cells is done on multiple scales of length and time. Despite recent progress in understanding the folding motifs of chromatin, the higher-order folding still remains elusive. Flourescent in situ hybridization reveals a tight connection between genome folding and function as well as a folding into a confined sub-space of the nucleus. The folding state of chromatin reveals distinct differences from a compact conformation. A previously published model, the random loop (RL) model, explains the folding state by the formation of random loops, which themselves seem to be an ubiquitous motif of transcriptional regulation. However, it remains a crucial question what mechanisms are necessary to make two chromatin regions become co-located, i.e. have them in spatial proximity.
The model presented here bridges the gap between statistical polymer models and an effective description of the dynamic process of loop formation mediated by the nuclear environment. Without assuming long-range forces or any active transport mechanisms, this model assumes that the formation of contacts or loops is done solely on the basis of random collisions. The probabilistic nature of the formation of temporary contacts mimics the effect of e.g. transcription factors in the solvent. Although only basic interactions are taken into account, this model is in agreement with recent experimental data.

2454-Pos
Prokaryotic Chromosome Organization in the Context of Entropy, Confinement and Tethering Interactions
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Prokaryotic chromosomes are physically organized and condensed into an intricately structured DNA-protein complex called a nucleoid. The large-scale physical structure might arise from protein mediated interactions that can form both inter and intra-chromosome tethers as well as anchoring the chromosome to the membrane of the nucleoid or to protein scaffolds [1]. Motivated by recent experiments that capture E. coli nucleoid structure using three spectrally distinct, fluorescently-labeled genetic loci [2], we analyze single-locus and two-locus positioning distributions in the theoretical framework of a coarse-grained polymer model taking into account excluded volume, confined geometries as well as tethering interactions therewith shedding light into the mechanisms governing E.coli nucleoid structure between replication cycles.
[1] W.F. Marshall, Current Biology 12, 158 (2002)
[2] P.A. Wiggins, K. Cheveralls, J.S. Martin, R. Lintner, J. Kondev, private communication